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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/944,326 | 08/30/2001 | Martin Gleave | UBC.P-020-2 | 2324 |

57381 7590 03/19/2007
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| EXAMINER |
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VIVLEMORE, TRACY ANN

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| ART UNIT | PAPER NUMBER |
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1635

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS | 03/19/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/944,326 | GLEAVE ET AL. | |
| | Examiner | Art Unit | |
| | Tracy Vivlemore | 1635 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 12, 13, 16, 19, 23-26 and 30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 19 and 30 is/are rejected.
- 7) ☒ Claim(s) 12, 13, 15 and 23-26 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

In view of the appeal brief filed on December 1, 2006, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:


J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 19 and 30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,900,187 in view of McKay et al. (US 5,877,309) and Cowser (US 5,945,920).

Claim 1 of the '187 patent is directed to an oligonucleotide consisting of the sequence of SEQ ID NO: 4 and having specific modifications of a phosphorothioate backbone, 2'-methoxyethyl modifications at each of the four terminal nucleotides with the remaining nucleotides being deoxynucleotides, and the modified nucleobase 5-methylcytosine at positions 1, 4 and 19. The pattern of 2'-substituted nucleotides flanking a region of deoxynucleotides recited in the claim of the '187 patent is known in the prior art as a gapmer. The specification of the '187 patent describes successful use of SEQ ID NO: 4 in both modified and unmodified forms.

The claims of the instant application are generic to the '187 patent, being directed to the oligonucleotide consisting of SEQ ID NO: 4 or a pharmaceutical composition comprising or consisting of SEQ ID NO: 4, with no requirement that the sequence be modified. The instant specification teaches at page 9:

The ODNs employed may be modified to increase the stability of the ODN *in vivo*. For example, the ODNs may be employed as phosphorothioate derivatives (replacement of a non-bridging phosphoryl oxygen atoms with a sulfur atom) which have increased resistance to nuclease digestion. MOE (2'-O-(2-methoxyethyl) modification (ISIS backbone) is also effective.

While the instant application explicitly suggests oligonucleotides may optionally be modified to improve stability *in vivo* and suggests the use of both phosphorothioates and 2'-methoxyethyl modifications, the instant application exemplifies use of unmodified

oligonucleotides and does not teach the use of a gapmer configuration or the presence of 5-methylcytosine nucleobases.

The use of modified nucleotides, including modified nucleobases, internucleotide linkages and 2-substituted sugars was well known in the art of antisense oligonucleotides at the time the instant application was filed. See, for example, McKay et al. and Cowsert.

McKay et al. teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). McKay et al. teaches such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. McKay et al. provide specific embodiments of such modifications at columns 6-8 and in Example 1. These specific examples taught by McKay et al. include the phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine nucleobases present in the '187 patent. At column 10 McKay et al. teach antisense oligonucleotides can be synthesized as chimeras, including the motif known as a gapmer, with 2'-substituted nucleotides flanking a deoxynucleotide core region. Tables 4, 5 and 11 show the successful design and use of modified oligonucleotides, including gapmers, in cells in culture. McKay et al. is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligonucleotides to target any known gene.

The teachings of Cowsert are considered to parallel those of McKay et al. Cowsert teaches general antisense targeting guidelines at columns 3-4. Cowsert

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teaches in columns 5-8 that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, modified sugar moieties including 2'-O-methoxyethyl, modified nucleobases including 5-methylcytosine, and teach these modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Table 1 teaches the successful targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-O-methoxyethyl modifications as present in the '187 patent. Thus, Cowser is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligonucleotides to target any known gene.

The claim of the '187 patent is an obvious variation of the instant claims.

The patented claim reciting specific modifications is an obvious variation of the instant generic claims because the instant application explicitly suggests modifying antisense oligonucleotides such as SEQ ID NO: 4 with phosphorothioates and 2'-methoxyethyl modifications at page 9. Based on the teachings of the antisense art as exemplified by McKay et al. and Cowser, it would also be obvious to use 5-methylcytosine nucleobases and a gapmer configuration of SEQ ID NO: 4 because both McKay et al. and Cowser teach and exemplify that gapmer oligonucleotides comprising 5-methylcytosines impart superior physical properties to an oligonucleotide as compared to unmodified oligonucleotides. The use of 5-methylcytosines at any particular position or combination of positions represents mere design choice made to

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provide an oligonucleotide having the best combination of properties for a desired application. Therefore, the claim of the '187 patent directed to the identical sequence of the instant application and comprising a pattern of modifications recognized by the art as providing desirable physical properties is an obvious variation of the instantly claimed sequence.

The instant generic claims are an obvious variation of the patented claim.

The instant claims that encompass both modified and unmodified sequences comprising SEQ ID NO: 4 are an obvious variation of the modified sequence of the '187 patent because the nucleotide sequences are identical and the person of ordinary skill, recognizing the teachings not only of the instant specification and the '187 specification of the effectiveness of SEQ ID NO: 4 when unmodified would recognize both modified and unmodified versions of SEQ ID NO: 4 are effective at inhibiting gene expression. Therefore it would have been obvious to make the unmodified form of SEQ ID NO: 4.

Response to Argument

Applicants argue the purpose of an obviousness type double patenting rejection is to prevent an applicant from having an unfair time-wise extension of patent term. It is noted in the instant case there is no question of extension patent term since both applications claim priority to the same date and any patent issuing from the instant application will expire on the same date as the '187 patent. However, extension of patent term is not the only reason to require a terminal disclaimer. A terminal disclaimer

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contains a provision that any patent granted on that application be enforceable only for and during the period that the patent is commonly owned with the application or patent which formed the basis for the rejection. These requirements serve to avoid the potential for harassment of an accused infringer by multiple parties with patents covering the same patentable invention. The instant application could provide such a situation. If the owner of this application were to receive two patents covering the claimed subject matter and they were sold separately the new owners could not only harass anyone accused of infringement but could potentially sue each other for infringement.

Applicants argue because the patent is the later filed application and the patent office controlled the speed of prosecution a two-way test is appropriate, referring to *In re Borah*, 148 USPQ 213 (CCPA 1966) to support their argument that a two-way test of obviousness should be applied. However, it is noted that the facts in this case are not completely identical to the instant situation. In *Borah*, the obviousness type double patenting rejection was applied in the third action and was applied only after the later filed application had issued as a patent. In the instant application, an obviousness type double patenting rejection has been present since the first action on the merits, first as a provisional rejection and later an obviousness type double patenting rejection after the '187 patent issued.

MPEP 804 requires a two-way test for obviousness only in situations where the claims conflict with those of a patent which has issued from a later filed application but also states even if the application at issue is the earlier filed application, only a one-way

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determination of obviousness is needed to support a double patenting rejection in the absence of a finding of: (A) administrative delay on the part of the Office causing delay in prosecution of the earlier filed application; and (B) applicant could not have filed the conflicting claims in a single (i.e., the earlier filed) application."

The MPEP further recognizes that determining whether or not there is administrative delay can sometimes be difficult. Therefore, although applicants have never demonstrated that the differing rates of prosecution in the two applications at issue constitute administrative delay on the part of the office, in the interests of advancing prosecution a two way showing of obviousness has been performed in the new rejection above.

Applicants further argue there has been no showing that the claims of the '187 patent are an obvious variation of the instant claims. The rejection has been re-written in order to address these arguments.

Applicants further argue the obviousness type double patenting rejection is inequitable because it penalizes the present applicants by placing them in a worse footing than if they had not invented the improvement of the '187 patent.

This argument is not understood because applicants do not describe how the requirement of a terminal disclaimer places them on "worse footing". Applicants argue the sequence of the '187 patent was of record in the parent case as 102(b) art. However, because the PCT application cited in applicants arguments is a parent of both the '187 patent and the instant applications, this PCT is in no way available as 102(b) art. Applicants further argue that the examiner of the '187 patent knew that the base

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sequence itself was known, but determined patentability without regard for the common inventors and common owners of the earlier patent application.

In response, the examiner would like to direct applicants' attention to guidance provided by the eighth edition, second revision of the MPEP that was in effect at the time the '187 patent was issued regarding provisional double patenting rejections.

MPEP 804 (I) B:

B. Between Copending Applications—Provisional Rejections

Occasionally, the examiner becomes aware of two copending applications filed by the same inventive entity, or by different inventive entities having a common inventor, and/or by a common assignee that would raise an issue of double patenting if one of the applications became a patent. Where this issue can be addressed without violating the confidential status of applications (35 U.S.C. 122), the courts have sanctioned the practice of making applicant aware of the potential double patenting problem if one of the applications became a patent by permitting the examiner to make a "provisional" rejection on the ground of double patenting. *In re Mott*, 539 F.2d 1291, 190 USPQ 536 (CCPA 1976); *In re Wetterau*, 356 F.2d 556, 148 USPQ 499 (CCPA 1966). The merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to issue.

The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

The first action on the merits for the instant application was mailed 2/17/2004 and contained a provisional obviousness-type double patenting rejection over the claims of 10/080,794, the application that resulted in the '187 patent. The notice of allowance for the '794 application was mailed almost 10 months later. Because the examiner of the '794 application had determined the claims to be patentable over the prior art and because office policy at the time stated that if a provisional double patenting rejection is the only possible rejection the application should be permitted to issue as a patent, the

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examiner of the '794 application was actually *precluded* from making an obviousness-type double patenting rejection in the '794 application. Therefore unless the prosecution history of the '794 application states otherwise, there is no basis for a conclusion that the examiner of the '187 patent determined patentability without regard for the common inventors and common owners of the earlier patent application.

Applicants further argue the examiner's refusal to comment on the prosecution of the '187 patent is itself a comment on the prosecution that indicates the examiner believes the other examiner was in error. The examiner strongly disagrees with applicants' interpretation of this situation. MPEP 1701 expressly states that PTO employees should not "express to any person any opinion as to the validity or invalidity of, or the patentability or unpatentability of any claim in any U.S. patent". If this guidance applied only to negative comments while allowing positive comments, a refusal to comment on prosecution of another application could indeed be interpreted as tacit expression of an opinion regarding validity of a patent. However the MPEP directs office employees to refrain from expressing any opinion and a refusal to comment cannot and should not be interpreted as a belief that the examiner of the '187 patent was in error.

Allowable Subject Matter

Claims 12-15, 24-26 and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

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folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
March 14, 2007

A handwritten signature in black ink, appearing to read 'R. Schnizer', with a stylized flourish at the end.

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER